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Tumor Suppression In Nude Mice By Radiotherapy With Rhenium-188 Labeled Somatostatin Receptor-Avid Peptides

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Technetium(Tc)-99m-labeled depreotide (NeoTect®), a cyclic dodecapeptide with high affinity for somatostatin receptors (SSTr), has been shown to detect SSTr-positive tumors in animal models and cancerous solitary pulmonary nodules in humans. We have evaluated the radiotherapeutic efficacy of Rhenium-188(Re-188)-depreotide and P773, a structural analog in nude mice bearing tumors derived from the human lung (NCI-H69) or rat pancreatic (AR42J) cancers. Both express high levels of SSTr's. Re-188 emits beta and gamma radiation ($t_{1/2}$=17hr) and has an outer electron shell nearly identical to Tc-99m. Thus, it undergoes chelation by P829 and P773 similar to Tc-99m except that extra stannous chloride is required.

Re-188 was eluted from a Tungsten-188/Re-188 generator (Oak Ridge), and added to standard kits used to radiolabel depreotide or P773 with Technetium-99m. Reconstituted kits were heated, filtered, and anti-oxidants added to prevent radiolysis. Radiochemical purity was $\geq$95% (by ITLC and HPLC). Re-depreotide and Re-P773 competed with ^{125}I-SST for specific binding to membranes from NCI-H69 with $IC_{50's}$ of 0.09 and 0.7 nM, respectively.

Female nude mice (CD1; Nu/Nu) were implanted with 1-3 million NCI-H69 or AR42J cells. Radiotherapy was initiated when the tumor volume was approximately 100 mm^3.

Two or three weeks after implantation of NCI-H69 cells, mice were randomly divided into three treatment groups: Re-188 P773 (Re-188-P773; 50 µCi, 1.2 µg per mouse), unlabeled peptide (P773 1.2 µg per mouse), untreated controls (No Rx). Mice were dosed intravenously (i.v.) and tumor volumes measured twice weekly (normalized to initial sizes) for 18 days. Average tumor size in the no Rx group increased 262%, compared to a 67% increase in the Re-188-P773 group over the same period ($p<0.02$). No suppression of tumor size was observed in mice that received unlabeled P773.

In studies with AR42J-derived tumors, 7 groups of mice were injected i.v. with either unlabeled depreotide (control 1), decayed Re-188 eluate (control 2), or Re-188-depreotide (50 µCi, 100 µCi, 250 µCi, 400 µCi or 500 µCi) every 4 days for 3 weeks.

Tumors grew over 30-fold in untreated control mice during the study period. No

therapeutic effect was observed in mice that received 50 of Re-188-P829. However, statistically significant ($p<0.05$) reduction in tumor growth (vs. controls) was observed at 18 days for mice receiving the other four Re-188-depreotide doses, with actual tumor regression occurring in several mice within the two highest doses. Tumor volumes in the five Re-188-depreotide groups averaged 3000%, 1000%, 500%, 86%, and 75% of initial volumes.

In conclusion, Re-188-depreotide dose-dependently suppressed tumor growth in SSTr-expressing tumors *in vivo*. Inasmuch as Tc-99m P829 has been shown to noninvasively identify cancerous lung tumors in humans, Re-188-P829 holds potential for radiotherapy in patients with scintigraphically positive lung tumors, identified with either Tc-99m-P829 or Re-188-depreotide.